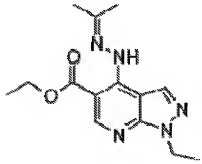
REMARKS

Reconsideration is requested.

The Section 103 rejection of claims 12-14 over Ikhlef (U.S. Patent Application Publication No. 2003/0064374) in view of Schumcher (U.S. Patent No. 7,153,871) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The claims define a method of improving perceptive cognition in a patient in need thereof, the method comprising administering to the patient an effective amount of etazolate, and monitoring said patient for improvement in perceptive cognition after said administering.

Etazolate has the following structure:



The rejection is understood to be based on an assertion that treating Alzheimer's disease would necessarily or inherently cause improvements in cognitive deficits , which are a symptom of Alzheimer's disease. The cited art fails to teach or suggest the claimed method which requires administration of an effective amount of etazolate to improve perceptive cognition in a patient.. The claims further require monitoring the treated patient for improvement in perceptive cognition after administering etazolate.

The primary reference (Ikhlef) teaches away from monitoring a treated patient for improvement in perceptive cognition after administering etazolate as Ikhlef teaches that an advantage of the Ikhlef method is not monitoring the symptoms accompanying the treated neurodegenerative disease. See ¶[0012] of Ikhlef. Ikhlef describes the discovery of a new molecular target (i.e., phosphodiesterase 4B (PDE4B)) for "detecting an excitotoxicity situation or neuronal stress in a subject" (see ¶[0013] of Ikhlef) whereby "the presence of a mutant RNA of phosphdiesterase 4, particularly phospodiesterase 4B, in a sample from the subject, in particular a form deleted of all or part of the 3' noncoding region" is detected. See ¶[0014] of Ikhlef. Ikhlef further describes as follows:

> "The invention also provides for new methods of diagnosis, screening, detection, determination of a predisposition or monitoring the progression or the efficacy of treatment of these diseases." See ¶[0012] of Ikhlef.
>
> "The invention is generally based on the use of a nucleic acid complementary to all or part of the PDE4B gene or messenger, for detecting pathological events related to excitotoxicity, stress, neuronal death, etc." See ¶[0016] of Ikhlef.

Ikhlef teaches away from the claimed method in that Ikhlef describes monitoring treatment with molecular markers relating to the PDE4B gene or messenger.

Ikhlef describes that the PDE4B marker was isolated from over 200 separate sequences involving "key players in the excitotoxicity phenomenon" (see ¶[0009] of Ikhlef) in a transgenic mouse model system of a familial form of Amyotrophic Lateral Sclerosis (FALS) involving expression of human superoxide dismutase 1 gene (SOD1) bearing one mutation (G93A).

There is no teaching or suggestion in Ikhlef that the Amyotrophic Lateral Sclerosis mutation of the transgenic mouse model of Ikhlef is related to diminished perceptive cognition in patients suffering from Alzheimer's disease. To the contrary, Ikhlef suggests that the relation between the PDE4B molecular target discovered by Ikhlef for treating ALS, and Alzheimer's disease is

> "based on the goal of reducing the inflammation observed in brain during neurodegenerative processes and not at all on a rationale aiming to directly inhibit neuronal death." See ¶[0019} of Ikhlef .

Ikhlef therefore fails to suggest monitoring patients after treatment as required by the claimed method and Ikhlef fails to teach or suggest treatment of perceptive cognition, such as by teaching or suggesting a connection or correlation between PDE4B expression and perceptive cognition.

The present Examiner's assertion that Ikhlef

> "teaches treating neurodegenerative diseases, including ALS and Alzheimer's disease with the use of etazolate, which is a PDE4 inhibitor" (see page 4 of the Office Action dated October 14, 2009)

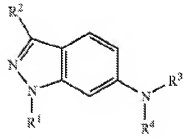
is contrary to Examiner Gibbs' assessment of Ikhelf that the reference failed to provide "guidance or example that would show by correlation the effects of any inhibitor, other than pentoxifylline", for the treatment of neordegenerative disease. See page 4 of the Office Action dated August 28, 2002 in application no. 09/983,754 (copy attached). Examiner Gibbs noted that "the scope of the instant invention is so broad as to include [treatment of] Alzheimer's disease and [I.e., with] etazolate". Id. Examiner Gibbs asserted that Ikhelf failed to teach one of ordinary skill in the art how to make and use

etazolate for the treatment of Alzheimer's disease without requiring undue experimentation.

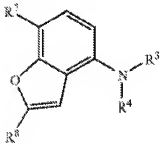
The Examiner's secondary reference (Schumcher), fails to cure the deficiencies of Ikhlef. Rather, Schumcher teaches the unpredictability of predicting the function of compounds used for treating Alzheimer's disease.

Schumacher relates to aminoindazole and aminobenzofuran analogs of the following formulas which inhibit PDE4:

I



II



These compounds are proposed for relieving loss of memory, such as long-term memory. These compounds, however, are structurally very remote from etazolate. Furthermore, these compounds also are functionally distinct since etazolate has been shown by the inventors to bind GABA receptors. Moreover, there are no experimental data which support any effect of these compounds on cognition.

The Examiner is understood to believe that it would have been obvious for the ordinarily skilled person

> "to have expected, with a reasonable degree of success, that a PDE4 inhibitor, namely etazolate, which is effective in treating Alzheimer's disease, can also be employed to improve cognition".

An ordinarily skilled person would not have inferred from Schumacher that every PDE4 inhibitor is suitable to improve perceptive cognition. As noted above, the compounds of Schumacher are structurally remote from etazolate and their activity on memory is not documented. Furthermore, treating Alzheimer's disease does not necessarily imply improving cognition. The applicants submit that if the link were as direct as the Examiner apparently believes, there would be many compounds on the market to treat cognitive deficits. The reality is very different. It was not obvious to have isolated and characterized a compound which can improve cognitive deficits.

The Examiner considers etazolate would have at least been regarded as a candidate to at least try in a method of improving cognition. The applicants respectfully submit however that there are thousands of PDE4 inhibitors in the literature and yet it would not have been obvious or reasonably predictable that there compounds would be useful candidates for improving cognition.

It is the discovery, by the applicants, that etazolate acts on GABAA receptors which has allowed the applicants to propose this molecule for treating cognitive deficits. It is the discovery that etazolate not only inhibits PDE4 but also modulates GABAA receptors, which has made etazolate a candidate for treatment of perceptive cognition. Until this mode of action was discovered, there was no objective reason to consider

etazolate as a reasonable candidate, or to propose this molecule for treatment of cognitive deficits.

The results presented by the applicants show that etazolate is a GABAA receptor modulator (see e.g., examples 1 and 2 of the application as well as the publication by Marcade et al previously submitted); that etazolate improves the mnestic and cognitive properties in aged rats (see e.g., Example 5 of the application); that etazolate improves attention, learning capabilities and cognitive behaviour (Barnes test, additional data submitted previously); and that etazolate reversed the deficit memory induced by scopolamine in rats (additional data submitted previously).

These results have further been confirmed in human beings. The applicants have recently completed a phase IIa clinical study in 197 patients. As disclosed in the attached press release, etazolate (referred to as EHT 202 in this release) exhibits "good safety and tolerability" and a "trend for efficacy on cognition was observed".

The activity of the etazolate towards cognitive deficits was not disclosed or suggested in the cited art nor suggested by any prior use of this compound or other PDE4 inhibitors. The results obtained by the applicant unexpectedly demonstrate the ability of this compound to treat cognitive disorders in vivo. It is therefore submitted that the claimed invention would not have been obvious in view of the cited art.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100